UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/662,783 | 09/12/2000 | Richard A. Shimkets | 15966-577 (CURA-77) | 3145 |

7590 08/27/2002

Mintz Levin Cohn Ferris
Glosky and Popeo P C
One Financial Center
Boston, MA 02111

| EXAMINER |
|---|
| JIANG, DONG |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 08/27/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/662,783 | SHIMKETS ET AL. | |
| | Examiner | Art Unit | |
| | Dong Jiang | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *6-39 and 41-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-65* are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED OFFICE ACTION**

Applicant's amendment in paper No. 9, filed on 05 June 2002 is acknowledged and entered. Following the amendment, claims 1-5 are amended.

Currently, claims 1-65 are pending, and claims 1-5 and 40 are under consideration.

Applicants traverse the restriction requirement between SEQ ID NO:2 and SEQ ID NO:4, and indicate that FCTR1 (SEQ ID NO:2) and FCTR2 (SEQ ID NO:4) are splice variants of a common gene, that, according to MPEP, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will be examined together, and that MPEP 803.04 states that normally ten sequences constitute a reasonable number for examination purposes. This argument is not persuasive for the following reasons: the instant invention is not directed to a nucleotide sequence encoding the same protein, rather, it is directed to two proteins encoded by the same gene. The two proteins are distinct because of their different sequence structures. A search of SEQ ID NO:4 may not reveal anticipatory references of SEQ ID NO:2 as SEQ ID NO:4 is only a portion of SEQ ID NO:2. Therefore, separated searches are required for SEQ ID NO:2 and SEQ ID NO:4, which would constitute an undue search burden on the examiner and the USPTO's resources. Further, currently, the policy of searching up to ten sequences in a single application is not implemented because of the limitation of the USPTO's resources. The partial waiver of restriction practice is not a requirement, but is available at the Examiner's diseretion. Given the exponential increase in commercial database size, it is no longer feasible to examine up to ten sequences per case.

The requirement is still deemed proper and is therefore made FINAL.

***Withdrawal of Objections and Rejections:***

The rejection of claims 1-5 and 40 under 35 U.S.C. 101, and 35 U.S.C. 112, first paragraph for lack of utility is withdrawn in view of applicants argument, further in view of the specification, and based on the fact that a p35 FCTRX protein is demonstrated to have specific biological activities, such as binding and phosphorylation of the PDGF alpha receptor (Example

14), and that the p35 fragments have been verified to be cleaved products, and are encompassed within SEQ ID NO:4 (Example 12).

***Formal Matters:***

***Priority***

This application claims priority to US provisional applications 60/158,803, 60/159,231, 60/174,485, 60/186,707, and 60/188,250. For the following reasons, the Examiner finds that the present claims 12-87 are not supported in the manner required by 35 U.S.C. 112, first paragraph by the prior applications, thus none of present claims is entitled to the benefit of the filling date of the prior applications.

The priority applications merely discloses two polypeptide sequences of SEQ ID NO:2 and 4. The latest prior application, 60/188,250, filed on 10 March 2000, teaches that based on their sequence homology to some human growth factor and to rat vascular endothelial growth factor D, the two polypeptides may serve as novel growth-modulating factor to which various cells and tissues in the human body respond. The prior applications fails to provide any specific, substantial and credible utility, and provides no guidance or working examples to teach how to used the claimed invention. Therefore, the Examiner is not able to establish that the priority document satisfies the utility/enablement requirement of 35 U.S.C. 101/112, first paragraph. As such, the claims of the instant application are not entitled to the benefit of the filling date of prior applications listed above.

***Specification***

The specification is objected to for the following informalities, and appropriate correction is required: at page 117, line 17 indicates "(see Table ***6***)", whereas there is no Table 6 in the specification, and at page 123, line 17, "the *two* bands" should be "the *three* bands".

***Claims***

Claim 5 is objected under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel

the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims depend from claim 1, which is drawn to an amino acid sequence of SEQ ID NO:4, a mature form thereof, a variant of a mature form, or a fragment thereof. Claim 5 is directed to a variant of claim 1, wherein the variant is embraced in claim 1, therefore, claim 5 is not further limiting claim 1.

***Objections and Rejections under 35 U.S.C. 112:***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, as amended, is indefinite because it is unclear what "a mature form" of SEQ ID NO:4 is (parts b) and c)). It is noted that a mature form of a FCTR1 is defined as having amino acids 24-370 of SEQ ID NO:2 in the specification (page 12, lines 28-29), there is no definition of such for SEQ ID NO:4 (FCTR2). As SEQ ID NO:4 merely comprises the C terminal portion of SEQ ID NO:2, the defined mature form for SEQ ID NO:2 cannot be used for SEQ ID NO:4. It is not clear what a naturally occurring polypeptide is, and how many mature forms may exist in nature. Furthermore, the product of recombinant expression may depend upon cell type used. The metes and bounds of the claimed mature form, therefore, cannot be unambiguously determined. The claim is further indefinite for the limitation of "a variant" (part c)) and "a fragment of SEQ ID NO:2" (part d)). As the claim does not define the type of variation, and the size, region, or the function of the fragment, it is unclear what variants or fragments are within the limitation of the claim.

Claim 2 is indefinite and confusing for reciting "a FCTR2 fragment of a FCTRX polypeptide". As FCTR2 represents a specific polypeptide, it is unclear how a FCTR2 fragment can be from any FCTRX polypeptide.

Claim 3 is indefinite because it is not clear what is meant by "naturally occurring". This appears to be product-by-process limitation but it is not clear what distinguishes a "naturally

occurring" polypeptide or polynucleotide from one that is not. The metes and bounds of the claim cannot be determined. For example, it is not clear if a polynucleotide produced by PCR but having the same sequence as a polynucleotide isolated from a natural source would be considered to be naturally occurring. The claim is further indefinite for reciting "said *polypeptide is a ... allelic variant*" as the term "allelic variant" is used to describe a gene (polynucleotide), not a polypeptide.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and the dependent claims 2-5 and 40 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to *a dimer (p35)* formed by bands I, II, and/or III, wherein bands I-III represent the three specific fragments of SEQ ID NO:4 (or SEQ ID NO:2), defined by Example 12 and Figure 10 of the specification, i.e., band I is 22-25 kDa with N-terminal beginning at residue 247 of SEQ ID NO:2, band II is about 16 kDa with N-terminal beginning at residue 247 of SEQ ID NO:2, and band III is about 5-6 kDa with N-terminal beginning at residue 339 of SEQ ID NO:2 (page 123, lines 17-20), does not reasonably provide enablement for claims to SEQ ID NO:4, a variant thereof (as claim 1, for example), and a fragment thereof (claims 1 and 2, for example). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1-5 and 40 are directed to a polypeptide of SEQ ID NO:4 (amino acid residues 239-270 of SEQ ID NO:2), a mature form, a variant, or a fragment thereof, which encompass

any or all variants and fragments, either with or without functional activity, such as a dipeptide. However, the specification merely teaches that *p35* protein has specific biological properties, and p35 is *a dimer* composed from a combination of three specific fragments of SEQ ID NO:4 (or 2), as cited above. The disclosure does not teach SEQ ID NO:4, nor any variant or fragment thereof, by themselves, have any biological function equivalent to that of p35 protein. Further, the specification does not teach the structural and functional relationship of the polypeptide, and provides no guidance as to which regions of the polypeptide would be tolerant of modification and which would not, or working examples of any variant or fragment sequence, which would be within the limitations of the claims. It is in no way predictable that SEQ ID NO:4 and randomly selected variants or fragments thereof, either by themselves or by any combination would have the activity comparable to the one disclosed for p35 protein. Undue experimentation would be required to determine the function of SEQ ID NO:4, and variants or fragments thereof, if they have any, and combinations of above to make a functional protein.

Furthermore, as no functional limitation is associated with the claimed polypeptides, the specification provides no guidance as to how the skilled artisan could use an inactive polypeptide variant or fragment of SEQ ID NO:4. Therefore, it would require undue experimentation to practice this invention as claimed, because the skilled artisan would have no reasonable expectation of being able to use the variants encoding polypeptides that are inactive for any purpose stated in the specification.

Due to the large quantity of experimentation necessary to determine an activity or property of the disclosed SEQ ID NO:4, and variants or fragments thereof, and any combination above to make a functional protein with desired activity, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, which requires a combination of two polypeptides to be functional, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural variants and fragments of SEQ ID NO:4, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicants argument, filed on 05 June 2002 (paper No. 9) has been fully considered, but is not deemed persuasive for reasons below.

At pages 6-7 of the response, the applicant argues that SEQ ID NO:4 or FCTR2 is a variant of FCTR1, and the 132 amino acids of SEQ ID NO:4 is 100% identical to the C terminal region of SEQ ID NO:2, accordingly, one of skill in the art would appreciate the significance in the region of overlap or identity of these sequences, how to make the claimed protein, and how to predict amino acid substitutions. This argument is not persuasive because as the overlapping regions between the two variants are 100% identical, there is no way of predicting the consequence of amino acid substitutions based on the sequence comparison. Additionally, as addressed above, the specification teaches that only p35 protein, *not* SEQ ID NO:2 or 4, or any fragments thereof by itself, has the disclosed biological properties. Therefore, it is unpredictable whether any of said variants or fragments would be functional, and there is no way of testing such as a biological function of SEQ ID NO:4 by itself is not disclosed in the specification.

Claims 1-5 and 40 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification discloses *two* amino acid sequence with particularity, FCTR1 and FCTR2 with SEQ ID NO:2 and 4, respectively, and three specific fragments of SEQ ID NO:4 (or 2). No other FCTR2 variants or fragments meeting the limitations of the claims were ever identified or particularly described.

The present claims 1-5 and 40 encompass significant structural variation within the claimed variants (claims 1, 3-5 and 40) and fragments (claims 1, 2 and 40) of SEQ ID NO:4. The claim limitations of claims 3 and 4 are directed to a naturally occurring allelic variant of SEQ ID NO:4, and a variant resulted from a single nucleotide polymorphism, respectively. The

specification discloses the polypeptide of SEQ ID NO:4. No allelic or polymorphism variants of SEQ ID NO:4 meeting the limitations of these claims were ever identified or particularly described. With the exception of SEQ ID NO:2 and 4, and the three specific fragments thereof ("bands I, II and III"), the skilled artisan cannot envision the detailed chemical structure of the encompassed various variants and fragments of SEQ ID NO:4, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Furthermore, as to the limitation of "a mature form" of amino acid sequence of SEQ ID NO:4 in claim 1, the specification provides no written description to define the term by the sequence structure, but merely indicates that SEQ ID NO: 4 is a splice variant of FCTR1 (SEQ ID NO:2), and comprises C terminal 132 amino acids of SEQ ID NO:2. A skilled artisan would not have known what is the mature form of SEQ ID NO:4, and how many mature forms may exist in nature without sequence definition.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO:4, and the three specific fragments thereof, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants argument, in paper No. 9 has been fully considered, but is not deemed persuasive for reasons below.

At pages 9 of the response, the applicant argues that determining allelic variation is known in the art, and a patent need not teach what is well known in the art, accordingly, one of skill in the art could readily produce allelic variants of the FCTRX protein following the

teachings in the specification. This argument is not persuasive because the claim is directed to a naturally occurring allelic variant, which is totally unpredictable. As the specification provides no written description of the sequence structure of such a variant, a skilled artisan cannot envision the detailed chemical structure, and would not be able to make said variant.

***Rejections Over Prior Art:***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Eriksson et al., WO200027879 (provided by applicants).

Eriksson discloses a human platelet derived growth factor, PDGF-D (SEQ ID NO:6 or 8), comprising the amino acid sequence of SEQ ID NO:4 of the present invention with 100% identity (see computer printout of the search results). Additionally, Eriksson teaches fragments (page 12, lines 19-25, and Example 2) and various variants of said polypeptide, including a polypeptide variant encoded by a naturally-occurring allelic variant with a single nucleotide variation (page 14, the second paragraph), a polypeptide variant comprising one or more conservative amino acid substitutions (page 13, line 32 to page 14, line 2, and page 45, lines 16-19), and a pharmaceutical composition of the polypeptide and a pharmaceutical acceptable carrier (page 23, the last paragraph). The reference, therefore, anticipates the present claims 1-5 and 40.

***Conclusion:***

No claim is allowed.

***Advisory Information:***

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CLAIRE KAUFMAN
PATENT EXAMINER

DJ
8/14/02